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Ranolazine and Silent Ischemia

I read with interest the paper by Stone et al. (1), in which the authors investigated the relationship between ST-segment depression and the rate-pressure product during exercise. Based on their findings, they suggested that ranolazine's beneficial action is most likely primarily due to improvement of regional coronary blood flow in areas of myocardial ischemia. I do not refute that statement, but I would like to remind the readers that the current hypothesis of the mechanism of action of ranolazine is that it works only after myocardial ischemia has been present. When that happens, the late sodium channel remains open, leading to intracellular sodium overload, and the sodium–calcium exchanger then leads to intracellular calcium overload, which results in increased calcium ions intracellularly and impaired diastolic relaxation and increased tension. Ranolazine inhibits the myocardial late inward sodium current associated with ischemia and thus breaks up the cycle (2).

The authors emphasize in their article that under low stress conditions of exercise where there was mild ischemia, the ranolazine did not seem to be effective; however, as the ischemia became more pronounced, the anti-ischemic effects of ranolazine became more marked.

My question to the investigators is this: Since it has been shown many times that patients with chronic stable angina have multiple episodes of asymptomatic cardiac ischemia, is it possible or probable that these multiple episodes of silent cardiac ischemia are prevented from becoming manifest symptoms of myocardial ischemia (i.e., angina) by the drug ranolazine?

I suspect that the only way one could find the answer is to have chronic ambulatory electrocardiogram (ECG) monitoring of these patients. I know that patients who were in the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Segment Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36) trial (3) had 7 days of ambulatory ECG monitoring, but the published study revealed that only arrhythmias were assessed. Would it be possible to go back and investigate those ambulatory ECGs to see whether or not silent ST-segment depression was present on several occasions without any manifestations of angina?

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Reply

Dr. Conti raises an interesting conceptual point regarding our paper (1) concerning the implications of treatment with ranolazine. If ranolazine were to render each ischemic episode less severe than an ischemic episode in the absence of ranolazine, then despite a reduction in symptomatic ischemia (i.e., angina), ranolazine may be associated with more frequent asymptomatic ischemia and, by inference, may expose the patient to an increased risk of cardiac events.

The fundamental premise implicit in this question, however, that asymptomatic episodes of myocardial ischemia represent less severe ischemia than symptomatic episodes, has not been demonstrated in any clinical study. Episodes of asymptomatic ischemia recorded during ambulatory electrocardiogram (ECG) recordings demonstrate the same ECG characteristics of ischemia severity as episodes of symptomatic ischemia (2). There is no evidence to support the notion that asymptomatic ischemia is asymptomatic because it is less severe than symptomatic ischemia and, consequently, does not reach an "angina threshold."

As Dr. Conti noted, patients in the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Segment Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36) trial had 7 days of continuous ECG recordings following admission with a non–ST-segment elevation acute coronary syndrome.

The TIMI (Thrombolysis In Myocardial Infarction) investigators did, in fact, assess ischemic episodes throughout the recording period and found that there was not a significant difference in the rate of positive ECG recordings for ischemia (19.9% on ranolazine vs. 21.0% on placebo; p = 0.21) (3). The investigators did not specifically report the individual number of symptomatic and silent episodes of myocardial ischemia or their duration during ECG monitoring on ranolazine versus placebo. The aggregate risk of cardiovascular death or myocardial infarction in the MERLIN–TIMI 36 trial was similar for patients taking ranolazine and placebo and in the patient subset that was enrolled with prior chronic angina, fewer recurrent ischemic episodes were observed in the ranolazine-treated group after 1-year follow-up, and exercise duration was significantly greater (4). Thus, the hypothesis that converting symptomatic to silent ischemic episodes with ranolazine is harmful is unlikely to be valid.

It would be interesting for the TIMI investigators to address the specific question of the proportion of the number and duration of asymptomatic and symptomatic ischemia episodes in patients taking ranolazine versus placebo from their extensive continuous ECG database and to correlate these findings with 1-year outcome. This type of analysis would expand our knowledge on ranolazine treatment effects and could potentially more completely address the question that Dr. Conti has raised.

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Clopidogrel After Coronary Artery Bypass Graft Surgery

Insufficient Evidence

We recently read the interesting study by Sørensen et al. (1), which evaluated the efficacy of clopidogrel after coronary artery bypass graft surgery (CABG) following a recent myocardial infarction (MI). Using data from 3,545 patients, the authors reported a lower risk of death and the combined endpoint of death or recurrent MI in patients who received clopidogrel after surgery. Based on their results, the authors recommend that a "focus on discharge clopidogrel treatment of these patients should be made" (1).

Because their study was nonrandomized, the authors used multivariate and propensity-score analyses to control for possible confounders. Interestingly though, no adjustment was made for the use of on- or off-pump CABG. In theory, any benefit associated with clopidogrel after CABG would be seen in an improvement in graft patency and the prevention of myocardial events. However, clopidogrel did not significantly reduce the incidence of recurrent MI, cardiovascular death, or the need for repeat revascularization in this study. How could clopidogrel lower the risk of death and yet not reduce the incidence of myocardial events after CABG? Although no explanation was provided by the authors, perhaps this finding relates to residual confounding. Clopidogrel may have been administered preferentially to healthier patients in this cohort who were believed to have a better chance for long-term survival.

Sørensen et al. (1) imply in their paper that clopidogrel is underused after CABG, referring to the current guidelines that recommend postoperative clopidogrel treatment for 9 to 12 months for patients who undergo CABG following MI (2). This recommendation was based primarily on data from the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial that reported significantly fewer adverse cardiac events among MI patients treated with the combination of clopidogrel and aspirin compared with aspirin alone, even if they ultimately underwent CABG (3). However, subgroup analysis later revealed that the benefit of combined antiplatelet therapy was entirely preoperative while patients were awaiting surgery. No benefit was seen for clopidogrel use after CABG in the CURE trial (4). Therefore, it is not surprising that many surgeons do not routinely prescribe clopidogrel after CABG.

Because of the lack of prospective data in the field (5), we recently performed the CASCADE (Clopidogrel After Surgery for Coronary Artery DiseasE) study (NCT00228423), a randomized, placebo-controlled trial to evaluate whether the addition of clopidogrel to aspirin would inhibit the process of saphenous vein graft disease after CABG (6). Compared with aspirin alone, the combination of aspirin plus clopidogrel did not significantly reduce vein graft intimal hyperplasia 1 year after CABG, as assessed by intravascular ultrasound. Although CASCADE was not powered for angiographic or clinical outcomes, we also did not see a significant difference in vein graft patency or cardiovascular events between the 2 treatment groups (7). Power calculations based on CASCADE determined that a sample size of 8,000 grafts would be required to demonstrate an improvement in patency with clopidogrel. We doubt a future trial of this size will ever be performed.

In summary, based on the data available to date, we do not believe that compelling evidence exists to support the routine use of clopidogrel after CABG.

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